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Synthesis of Anthradan analogues by regioselective Friedel–Crafts reactions on *N*,*N*-dihexylanthracen-2-amine

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ABSTRACT

An efficient synthetic route using a Friedel–Crafts acylation approach was developed to obtain fluorophores such as 1-(6-(dihexylamino)anthracen-1-yl)propan-1-one **(1b)** and 1-(7-(dihexylamino)anthracen-1-yl)propan-1-one **(1c)** with a push–pull electronic conjugation starting from 2-aminoanthracene-9,10-dione **(4)**. These compounds are analogues of 1-(6-(dihexylamino)anthracen-2-yl)propan-1-one (Anthradan) and they exhibit the same additional redshift emission and absorption spectra. Furthermore, we have synthesized other derivatives of Anthradan via the Friedel–Crafts approach in good yields.

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Fluorescent probes are compounds widely used as tools for diagnosis and monitoring of various diseases.[1] Lu et al. introduced the fluorophore 1-(6-(dihexylamino)anthracen-2-yl)propan-1-one (Anthradan).[2] This compound is a push–pull charge-transfer chromophore with an electron-donating dihexylamino group and an electron-withdrawing propionyl group located at the 2,6-positions of the anthracene ring (Fig. 1). Other related compounds generally employed as fluorescent probes include 2-propionyl-6-dimethylaminonaphthalene (PRODAN),[3] 6-acryloyl-2-dimethylaminonaphthalene (ACRYLODAN),[4] 6-lauroyl-2-dimethylaminonaphthalene (LAURDAN),[5] 2-(*N*,*N*-dimethylamino)-6-naphthoyl-4-trans-cyclohexanoic acid (DANCA),[6] 7-aryl-3-hydroxychromones,[7] and 3-methoxychromones.[8]

The most common fluorophores used in this type of procedure are anthracene derivatives, because they exhibit good emission properties with moderate to high quantum yields.[1a] These compounds have all the desired spectroscopic requirements for biological applications as well as absorption in the visible region (>400 nm), high absorption coefficient (>30,000 M^{-1} cm^{-1}), high fluorescence quantum yield (>50%) and photostability, with a strong solvatochromism.[9] This intrinsic alteration of the absorption and/or emission properties of a chromo(fluoro)phore is due to the influence of its molecular environment and the supporting solvent. Anthradan showed a significantly redshifted absorption and emission (around 460 nm) with a low absorption coefficient (12,000 M^{-1} cm^{-1}). However, the preparation of Anthradan involves a multistep synthesis with low overall yield and high cost of reactants, which are major drawbacks limiting its use in large scale applications such as forensics.[2,10,11]

The interest in fluorescent dyes for single-molecule fluorescence spectroscopy in biologically relevant systems led us to explore the synthesis of anthracene analogues of Anthradan. The push–pull structures of 1,6-substituted and 1,7-substituted anthracene derivatives would retain the useful properties found in Anthradan such as polarity-induced shift of emission and sensitivity to local nanoenvironments, and thus shifting the absorption further to the red which will improve results in cellular imaging. In Anthradan, the dihexylamine group was attached in order to enhance the solubility in ordinary organic solvents without significantly influencing the absorption and emissions spectra. The same properties were observed with the dimethylamino group in the PRODAN structure.

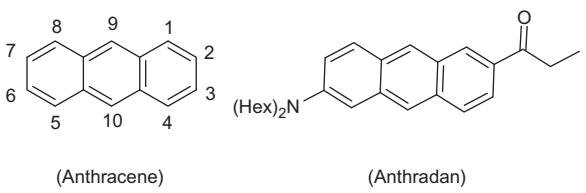

Figure 1. Anthracene and 1-(6-(dihexylamino)anthracen-2-yl)-propan-1-one (Anthradan).

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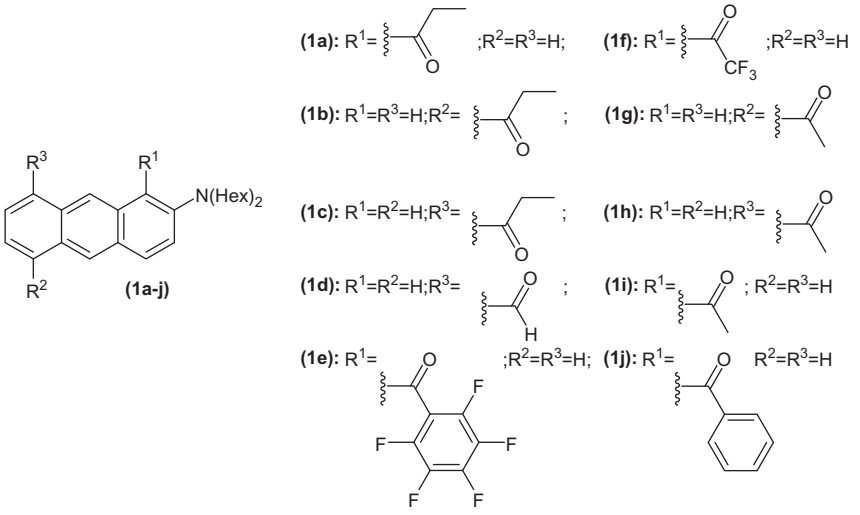
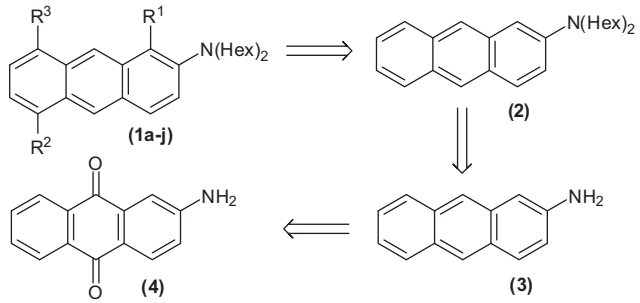
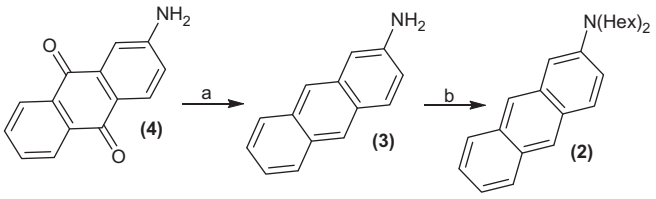


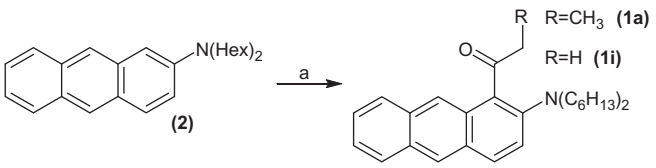
Figure 2. Donor–acceptor-substituted anthracene derivatives (**1a–j**).



Scheme 1. Retrosynthetic analysis of asymmetric push–pull anthracene derivatives (**1a–j**).

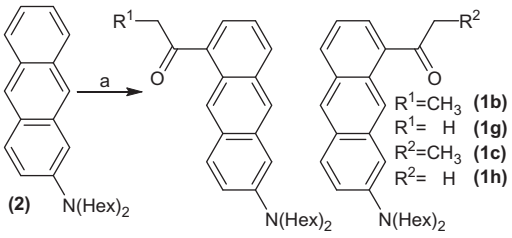


Scheme 2. Reagents and conditions: (a) Zn, NaOH, reflux 24 h (85%); (b) 1-Iodohexane, K_2CO_3, ethanol, reflux 24 h (90%).

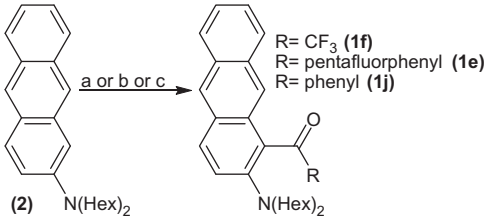


Scheme 3. Reagents and conditions: (a) Acetyl chloride or propionyl chloride, $AlCl_3$, 1,2-dichloroethane, 0 °C, 85% (**1a**) and 83% (**1i**).

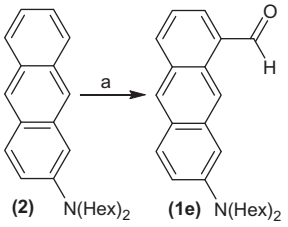
As we searched for an efficient fluorescent probe whose emission properties may be modulated by their environment, we prepared 10 analogues of Anthradan (Fig. 2) as part of a forensic program of research with the main objective to introduce new compounds for the formulations of invisible inks used in marking currency notes.[12]



Scheme 4. Reagents and conditions: (a) Acetyl chloride or propionyl chloride, $AlCl_3$, 1,2-dichloroethane, 40 °C, 92% (**1b**:**1c**, 46%:46%) and 90% (**1g**:**1h**, 45%:45%).



Scheme 5. Reagents and conditions: (a) TFAA, 0–40 °C, (90%); (b) pentafluorbenzoyl chloride, $AlCl_3$, 1,2-dichloroethane, 0–40 °C, (80%); (c) benzoyl chloride, $AlCl_3$, 1,2-dichloroethane, 0 °C, (80%).



Scheme 6. Reagents and conditions: (a) $POCl_3$, DMF, 150 °C, 70%.

Herein we report the straightforward synthesis and some physical properties of these new anthracene derivatives **(1a–j)** including the first examples of 1,2-acceptor–donor, 1,6-acceptor–donor, and 1,7-acceptor–donor Anthradan analogues. Our

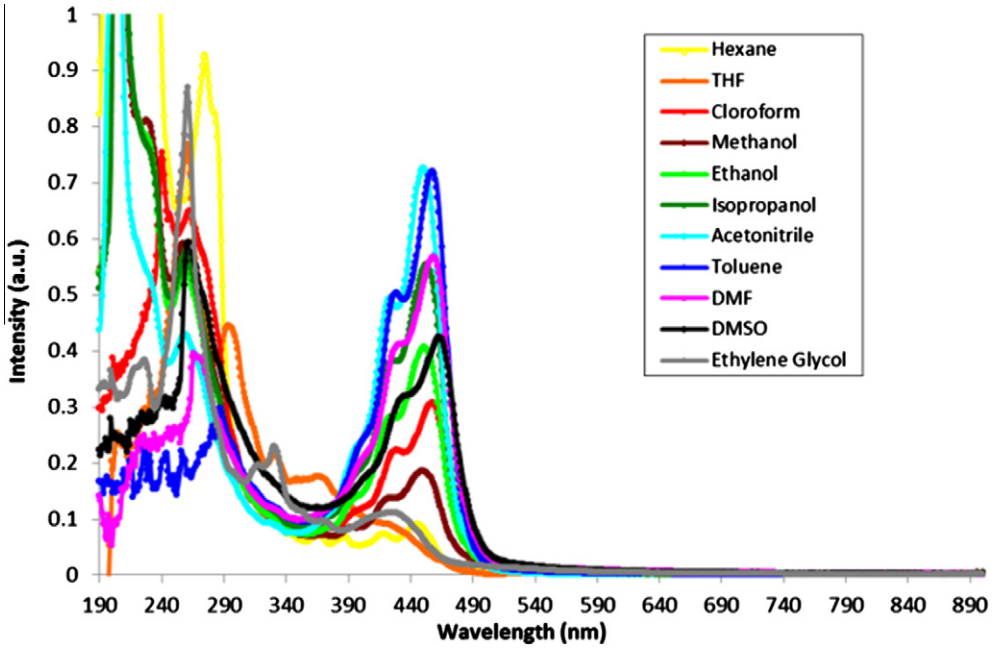


Figure 3. Absorption spectra of **1d** in hexanes, THF, chloroform, methanol, ethanol, isopropanol, acetonitrile, toluene, DMF, DMSO, and ethylene glycol.

Table 1
Absorption/emission of Anthradan, **2** and **1a–f** in different solvents[a]

Fluorophore solvent	1a	1b	1c	1d	1e	1f	2	Antradan[b]
n-Hexane	380/435	431/575	446/595	446/510	381/507	423/510	423/510	439/483
Toluene	456	459	455	458	390	428	390	447
Chloroform	455/519	450/561	458/586	457/514	394/493	434/499	431/490	458/536
THF	381	449	446	421	434	429	429	450
Acetonitrile	449/501	449/568	448/601	451/512	392/510	430/513	390/508	455/557
DMF	458	451	450	459	410	433	390	458
DMSO	463	463	462	463	429	436	390	460
1-Propanol	451	448	449	453	419	425	390	456
Ethanol	451/479	445/506	451/523	451/—	426/463	424/479	390/463	452/601
Methanol	449	456	448	450	419	425	390	456
Ethyleneglycol	361	453	468	426	448	432	430	464

[a] The concentration for absorption measurement was 10^{-5} M. The concentration for emission measurement was 10^{-7} M, and the excitation wavelength was at the absorption λ_{max}.
[b] Data for Anthradan are from Ref. 2

retrosynthetic analysis for the preparation of asymmetric anthracenes **(1a–j)** (Scheme 1) is based on regioselective acylation of the commercially available 2-aminoanthracene-9,10-dione **(4)**. DFT calculations at the B3LYP 6-31G* level on *N*,*N*-dihexylanthracen-2-amine **(2)** indicated that the carbon atoms at C-1, 5, and 8 are susceptible to eletrophilic attack. We believed the regioselectivity could be switched between these positions by carrying on the reactions under thermodynamic or kinetic control.

It should be pointed out that the susceptibility of positions 1, 5, and 8 to electrophilic attack can be explained in terms of stable resonance structures. Electrophilic attack at position 1 involves breaking the aromaticity at one ring and gives rise to the kinetic product. On the other hand, reactivity at positions 5 and 8 leads to very stable canonical forms and is the result of thermodynamic control at higher temperatures.

We began our synthetic work by reducing the 9,10 dicarbonyls in 2-aminoanthracene-9,10-dione **(4)**. Vigorous stirring with zinc dust in aqueous sodium hydroxide[13] solution afforded the desired anthracen-2-amine **(3)** in 85% yield. In the second step, *N*,*N*-dihexylanthracen-2-amine **(2)** was obtained in good yield (90%) by refluxing anthracen-2-amine **(3)** in a suspension of 1-iodohexane and potassium carbonate in ethanol (Scheme 2).[14]

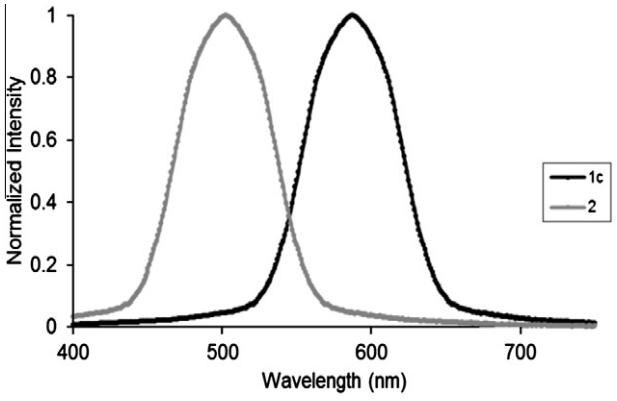


Figure 4. Normalized fluorescence spectra of **1c** (10^{-7} M) and **2** (10^{-7} M) in hexane.

Amine **(2)** was subjected to the traditional conditions of Friedel–Crafts acylation[15] with propionyl or acetyl chloride using aluminum chloride as Lewis acid at 0 °C in 1,2-dichloroethane. We obtained 1-(2-(dihexylamino)anthracen-1-yl)propan-1-one

(1a) and 1-1-(2-(dihexylamino)anthracen-1-yl)ethanone **(1i)** in 85% and 83% yields, respectively (Scheme 3).

When the Friedel–Crafts acylation was repeated at a higher temperature of 40 °C, a separable mixture of two equal isomers of 1-(6-(dihexylamino)anthracen-1-yl)propan-1-one **(1b)** and 1-(7-(dihexylamino)anthracen-1-yl)propan-1-one **(1c)**, were obtained in 46% yield. We also obtained 45% each of 1-(6-(dihexylamino)anthracen-1-yl)ethanone **(1g)** and 1-(7-(dihexylamino)anthracen-1-yl)ethanone **(1h)**, (Scheme 4).

However, when *N*,*N*-dihexylanthracen-2-amine **(2)** was treated with more reactive electrophiles such as trifluoroacetic anhydride or pentafluorbenzoyl chloride and aluminum chloride at 0–40 °C, we obtained only a single regioselective acylation of 1-(2-(dihexylamino)anthracen-1-yl)-2,2,2-trifluoroethanone **(1f)** and (2-(dihexylamino)anthracen-1-yl)(perfluorophenyl)-methanone **(1e)** in 80% and 90% yields, respectively. Another Friedel–Crafts reaction on *N*,*N*-dihexylanthracen-2-amine **(2)** was performed with benzoyl chloride and aluminum chloride as Lewis acid at 0 °C in 1,2-dichloroethane. We obtained (2-(dihexylamino)anthracen-1-yl)(phenyl)methanone **(1j)** with 80% yield. However, the same reaction when conducted at 40 °C produces a complex mixture of products together with a small amount of starting material.

All the three procedures above led to the kinetic products (**1e**, **f**, and **j**), which were formed by the attack of the electrophilic species at position 1 of *N*,*N*-dihexylanthracen-2-amine **(2)**, and no thermodynamic products arising from attack at position 5 or 8 were observed (Scheme 5).

Finally, the anthracene derivative 7-(dihexylamino)anthracene-1-carbaldehyde **(1d)** was obtained by the Vilsmeier–Haack reaction[16] of *N*,*N*-dihexylanthracen-2-amine **(2)** with $POCl_3$ and DMF at 150 °C (Scheme 6). All new compounds were characterized by ^1H and ^{13}C NMR, IR, and high-resolution mass spectroscopy.

The absorption spectrum of compound **1d** (Fig. 3) is characteristic of substituted anthracene derivatives with a donor–acceptor system that is dependent on the solvent properties unlike anthracene structures without the push–pull conjugation. The broad band around 390–540 nm is assigned as an intramolecular charge-transfer band.[2] The maximum charge-transfer molar extinction coefficients of **1a–f** in THF are 5.53×10^3; 3.53×10^3; 9.55×10^3; 9.16×10^3; 5.54×10^3; 1.13×10^4 L cm^{-1} mol^{-1}, respectively.

The maximum absorption of compounds **1a–f** (Fig. 3) in a variety of solvents spanning a wide range of polarity including nonpolar, polar and polar aprotic solvents are listed in Table 1.

The influence of selected solvents on the absorption of **1d** is shown in Figure 3. In contrast to the absorption, solvent polarity has a dramatic effect on the emission wavelength. Thus, an increase in solvent polarity causes a redshift of the emission band. This effect is especially pronounced for **1c** (Fig. 4) and leads to the conclusion that the dipole moment of the excited state is larger than the ground state (Table 1).[17]

In summary, we have prepared novel environment-sensitive fluorophores 1-(2-(dihexylamino)anthracen-1-yl)propan-1-one **(1a)**, 1-(6-(dihexylamino)anthracen-1-yl)propan-1-one **(1b)**, and 1-(7-(dihexylamino)anthracen-1-yl)propan-1-one **(1c)** and other compounds with 1,2-dipolar, 1,6-dipolar, and 1,7-dipolar anthracene fluorophores by a simple and straightforward synthesis. These compounds have a bathochromic shifted absorption and emission when compared to anthracene. The new fluorophores retain the same absorption and emission properties observed with Anthradan.

To demonstrate their potential, the isomeric mixtures of 1-(6-(dihexylamino)anthracen-1-yl)propan-1-one **(1b)**:1-(7-(dihexylamino)anthracen-1-yl)propan-1-one **(1c)**, and 1-(6-(dihexylamino)anthracen-1-yl)ethanone **(1g)**:1-(7-(dihexylamino)anthracen-1-yl)ethanone **(1h)** were used in a formulation of two invisible inks to mark currency notes and paper.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.085.

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